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Docket No. 75N-183H
Topical Antimicrobial Drug Products for Over-the Counter Human Use;
Health-Care Antiseptic Drug Products; Reopening of the Administrative Record

Dear ladies and gentlemen,

On May 28, 2003 the Department of Health and Human Services has displayed the reopening of the above mentioned administrative record.

We have the pleasure to submit some comments, which we hope will further improve the tentative final monograph for health-care antiseptic drug products.

If you have any questions, please do not hesitate to contact us.

Best regards,

BODE Chemie GmbH & Co.

Dr. Sabine Kühn
Marketing

Dr. Günter Kampf
Scientific Affairs

Enclosures

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Re: Reopening of the administrative record "health-care antiseptic drug products"
Docket No. 75N-183H

Introduction

BODE CHEMIE is one of Europe's leading manufacturer of modern, user-oriented products in infection control, medical skin care and technical preservation.

With our high performance products we place great value on professional quality management (DIN ISO 9001 and DIN EN 46 001), particularly as a manufacturer of drug registered products, medical devises and cosmetics. Our production processes are strictly in accordance with the German Medicines Act and GMP guidelines, as well Canadian GMP. Our FDA registered products are produced under FDA requirements using external production facilities.

All of our products, in which microbiological efficacy is in the foreground, are well characterized, and analyzed by well known and recognized external experts and laboratories. Depending on the specific requirements, our antiseptics and disinfectants are tested according to the appropriate test procedures, like European standards, or country-specific requirements.

To develop and manufacturer constantly high-quality products, scientist from a very broad range of disciplines are involved. Additionally, intensive opinion exchanges with clients, external experts, and research centers on international level, active participation or even organizing congresses contribute considerably to meet market needs today and in the future.

Only this year the 7th International BODE Hygiene Days took place in Spain, where international recognized experts in infection control (among others: e.g. J. Boyce, D. Pittet, M. Rotter, A. Widmer, W. Rutula) participated. Shortly these presented data will be published as a supplement in Journal of Hospital Infection. The supplement from the previous International BODE Hygiene Days is enclosed for your information. Additionally, as an initiative of BODE, last year a textbook about "hand hygiene in health care" (publishing house: Springer, editor: G. Kampf) has been published, which will coming soon as an English edition too. Three chapters have been written by J. Boyce and D. Pittet, authors of the new CDC guideline on hand hygiene.

Based on our experinences for years about antiseptic drug products we would like to take the opportunity to submit a few suggestions or comments to support you in developing the final monograph for health care antiseptic drug products in some specific points.

Comments

1. **<u>Hand antiseptics with more than one active agent</u>**

   We certainly agree that preparations based on single active agent have their place and are in various terms easier to assess, and our intension is not to change the current system by categorizing single active agents in a certain range of concentrations as safe and effective. However, for some clinical indications, a combination of active agents may reveal advantages. One advantage may be a superior antimicrobial efficacy, e. g. in surgical hand disinfection. This has been recently shown in a study on five different

preparations for surgical hand disinfection (1).

Some products have passed a European mutual recognition procedure for marketing authorization and have been classified as safe and effective throughout the European Union. In such a case we consider the effectiveness and safety similar to single active agents that have been classified by the FDA as safe and effective. We would therefore very much appreciate if such products could be registered by the FDA based on an European marketing authorization without a new drug approval (NDA).

2. **Test methods for hand rubs**

The current *in-vivo* test methods and their requirement requested in the current tentative final monograph are primarily designed to check the antimicrobial efficacy of hand wash preparations. Due to the study design leave-on products like alcoholic hand rub preparations have a methodological disadvantage: repetitive bacterial contamination of the hands without washing off the debris between recontamination results in cumulation of cell debris of the hands. Substanciated in the use of wash preparation like medicated soap, bacteria and cell depris are physically removed by using water after each recontamination cycle

We therefore suggest to incorporate additional test methods which are particularly suitable to assess the antimicrobial efficacy for hand rub preparations. A test method, classified as European Norm (EN) called "EN 1500", may serve as an example for such a new test method (2). It has been described to have an excellent intra- and interlaboratory reproducibility (3, 4). A similar test model exists also specific for surgical hand rub preparations (5). This test model has as well been shown to have an excellent reproducibility (6).

Both test methods have one test principal in common: Comparison of a test preparation with a reference treatment. The reference treatment was established based on a meta-analysis of efficacy data (7). We would appreciate a comparable test method with the same test principal in the FM, with the requirement: a test preparation shall not be significantly less effective than a well established reference. This would allow health-care workers a better comparission of products in the same product category (scrub or rub).

3. **Persistant efficacy in surgical hand disinfection (6 hour value)**

In the current tentative final monograph a 6 hour value on the gloved hand is requested. To our knowledge, the clinical relevance of a 6 hour value is scientifically not proven. Most surgical interventions are shorter than 6 hours. In general, as longer a surgical intervention lasts, a perforation of a surgical glove is more and more likely. A recent meta-analysis of surgical glove perforation has described a 18 % perforation of surgical gloves (8). In such a case it is highly recommended that the surgeon carries out a second surgical hand disinfection before putting on a new pair of gloves.

That is why from our point of view a 6 hour persistant efficacy is not really necessary. As an example: in Europe a 3 hour value has to be measured. This may serve as an example for a revised measurement of persistant efficacy.

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4. **Spectrum of bactericidal activity (time kill tests)**

In the current tentative final monograph a list of several bacterial species have to be tested. In addition, each species shall be tested with 25 clinical isolates and 25 specific strains. We understand these requirements are necessary to check the spectrum of antimicrobial activity of different active ingredients. With commonly used alcohol-based hand rubs, which are denaturing proteins and therefore act nonspecific on germs, this enormous testing of bacterial species and strains will quite certainly not lead to a better standard. In a recent study a selection of 2 gram positive test strains and 2 gram negative test strains was found to be valid to determine a general bactericidal activity, (especially in comparison to the selection of species of the tentative final monograph and in addition to some emerging pathogens (9).

Based on these data we suggest to reduce the number of bacterial species which have to be tested.

5. **Label claims of antimicrobial activity**

Health care workers in hospitals often need to know wheather a general activity against a specific group of microorganisms is given by the preparation used for hand antisepsis. The antimicrobial activity is typically classified in:

Bactericidal, tuberculocidal, fungicidal, virucidal (coated and/or uncoated viruses) and sporocidal.

This type of information on the label in combination with the appropriate killing-time would be a helpful information for the health-care personal and clarify an appropriate use of different formulations (e.g. if the application time is beyond the typical clinical use of a preparation (normally 30 sec)). The need for such label claims has recently also been emphasized by Professor Sattar (10).

6. **Confirmation of receipt**

If a preparation is registered with the FDA based on the tentative final monograph and the appropriate registration sheets are filled in and submitted to the FDA, it would be very much appreciated to receive a written conformation of receipt.

Dr. Sabine Kühn
Marketing

Dr. Günter Kampf
Scientific Affairs

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